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(21) International Application Number: PCT/US93/07149 (22) International Filing Date: 29 July 1993 (29.07.93) (30) Priority data: 07/923,401 31 July 1992 (31.07.92) US (60) Parent Application or Grant (63) Related by Continuation US 07/923,401 (CIP) Filed on 31 July 1992 (31.07.92) (71) Applicant (for all designated States except US): GENENTECH, INC. [US/US]; 460 Point San Bruno Boulevard, South San Francisco, CA 94080 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only) : O'CONNOR, Barbara, H. [US/US]; 150 Dale Avenue, San Carlos, CA 94070 (US). OESWEIN, James, Q. [US/US]; Post Office Box 13, Moss Beach, CA 94038 (US). (74) Agents: FITTS, Renee, A. et al.; Genentech, Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080 (US). (81) Designated States: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, NO, NZ, PL, RO, RU, SD, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: HUMAN GROWTH HORMONE AQUEOUS FORMULATION (57) Abstract A stable pharmaceutically acceptable aqueous formulation containing human growth hormone, a buffer, a non-ionic surfactant, and, optionally, a neutral salt, mannitol, or, a preservative, is disclosed. Also disclosed are associated means and methods for preparing, storing, and using such formulations.		

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HUMAN GROWTH HORMONE AQUEOUS FORMULATION

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Field of the Invention

The present invention is directed to pharmaceutical formulations containing human growth hormone (hGH) and to methods for making and using such formulations. More particularly, this invention relates to such pharmaceutical formulations having increased stability in aqueous formulation.

15 Background of the Invention

Human growth hormone formulations known in the art are all lyophilized preparations requiring reconstitution. Per vial, Protropin® hGH consists of 5 mg hGH, 40 mg mannitol, 0.1 mg monobasic sodium phosphate, 1.6 mg dibasic sodium phosphate, reconstituted to pH 7.8 (Physician's Desk Reference, Medical Economics Co., Orawell, NJ, p. 1049, 1992). Per vial, Humatrope® hGH consists of 5 mg hGH, 25 mg mannitol, 5 mg glycine, 1.13 mg dibasic sodium phosphate, reconstituted to pH 7.5 (Physician's Desk Reference, p. 1266, 1992).

For a general review for growth hormone formulations, see Pearlman et al., Current Communications in Molecular Biology, eds. D. Marshak and D. Liu, pp. 23-30, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989. Other publications of interest regarding stabilization of proteins are as follows.

35 U.S. 4,297,344 discloses stabilization of coagulation factors II and VIII, antithrombin III, and plasminogen against heat by adding selected amino acids such as glycine, alanine, hydroxyproline, glutamine, and aminobutyric acid, and a carbohydrate such as a

monosaccharide, an oligosaccharide, or a sugar alcohol.

U.S. 4,783,441 discloses a method for the prevention of denaturation of proteins such as insulin in aqueous solution at interfaces by the addition of up to 500 ppm surface-active substances comprising a chain of alternating, weakly hydrophilic and weakly hydrophobic zones at pH 6.8-8.0.

U.S. 4,812,557 discloses a method of stabilization of interleukin-2 using human serum albumin.

European Patent Application Publication No. 0 303 746 discloses stabilization of growth promoting hormones with polyols consisting of non-reducing sugars, sugar alcohols, sugar acids, pentaerythritol, lactose, water-soluble dextrans, and Ficoll, amino acids, polymers of amino acids having a charged side group at physiological pH, and choline salts.

European Patent Application Publication No. 0 211 601 discloses the stabilization of growth promoting hormones in a gel matrix formed by a block copolymer containing polyoxyethylene-polyoxypropylene units and having an average molecular weight of about 1,100 to about 40,000.

European Patent Application Publication No. 0 193 917 discloses a biologically active composition for slow release characterized by a water solution of a complex between a protein and a carbohydrate.

Australian Patent Application No. AU-A-30771/89 discloses stabilization of growth hormone using glycine and mannitol.

U.S. 5,096,885 (which is not prior art) discloses a formulation of hGH for lyophilization containing glycine, mannitol, a non-ionic surfactant, and a buffer. The instant invention provides an unexpectedly stabilized

aqueous formulation in the absence of glycine.

hGH undergoes several degradative pathways, especially deamidation, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Many of these reactions can be slowed significantly by removal of water from the protein. However, the development of an aqueous formulation for hGH has the advantages of eliminating reconstitution errors, thereby increasing dosing accuracy, as well as simplifying the use of the product clinically, thereby increasing patient compliance. Thus, it is an objective of this invention to provide an aqueous hGH formulation which provides acceptable control of degradation products, is stable to vigorous agitation (which induces aggregation), and is resistant to microbial contamination (which allows multiple use packaging).

Summary of the Invention

One aspect of the invention is a stable, pharmaceutically acceptable, aqueous formulation of human growth hormone comprising human growth hormone, a buffer, a non-ionic surfactant, and optionally, a neutral salt, mannitol, and a preservative.

A further aspect of the invention is a method of preventing denaturation of human growth hormone aqueous formulations comprising mixing human growth hormone and a non-ionic surfactant in the range of 0.1-5% (w/v) (weight/volume). In yet another aspect of the invention, this stabilized formulation is stored for 6-18 months at 2-8°C.

Description of the Figures

Figure 1 is a size exclusion chromatogram of aqueous growth hormone formulation stored for 28 days at 40°C (i.e., thermally stressed) and for one year at 5°C (i.e.,

recommended conditions for storage).

Figure 2 is a plot of Arrhenius rate analysis of growth hormone aggregation in aqueous formulation.

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Figure 3 is an anion exchange chromatogram comparing a thermally stressed (40°C) aqueous formulation hGH sample with an aqueous formulation hGH sample stored under recommended conditions (2-8°C) for one year.

10

Figure 4 is a plot of Arrhenius rate analysis of hGH deamidation in aqueous formulation.

Figure 5 is a graph of the percentage monomer present in the various formulations where mannitol has been substituted with a neutral salt.

Detailed Description of the Invention

20 A. Definitions

The following terms are intended to have the indicated meanings denoted below as used in the specification and claims.

25

The terms "human growth hormone" or "hGH" denote human growth hormone produced by methods including natural source extraction and purification, and by recombinant cell culture systems. Its sequence and characteristics are set forth, for example, in Hormone Drugs, Gueriguian et al., U.S.P. Convention, Rockville, MD (1982). The terms likewise cover biologically active human growth hormone equivalents, e.g., differing in one or more amino acid(s) in the overall sequence. Furthermore, the terms used in this application are intended to cover substitution, deletion and insertion amino acid variants of hGH, or posttranslational modifications. Two species of note are the 191 amino acid native species (somatropin) and the 192 amino acid N-terminal methionine (met) species (somatrem)

commonly obtained recombinantly.

The term "pharmaceutically effective amount" of hGH refers to that amount that provides therapeutic effect in an administration regimen. The compositions hereof are prepared containing amounts of hGH at least about 0.1 mg/ml, upwards of about 10 mg/ml, preferably from about 1 mg/ml to about 20 mg/ml, more preferably from about 1 mg/ml to about 5 mg/ml. For use of these compositions in administration to human patients suffering from hypopituitary dwarfism, for example, these compositions contain from about 0.1 mg/ml to about 10 mg/ml, corresponding to the currently contemplated dosage regimen for the intended treatment. The concentration range is not critical to the invention, and may be varied by the clinician.

B. General Methods

The instant invention has no requirement for glycine. Glycine is an optional component of the aqueous formulation, although with less advantage in the aqueous formulations hereof compared with those formulations that are lyophilized for later reconstitution. Amounts of glycine will range from 0 mg/ml to about 7 mg/ml.

Non-ionic surfactants include a polysorbate, such as polysorbate 20 or 80, etc., and the poloxamers, such as poloxamer 184 or 188, Pluronic® polyols, and other ethylene/polypropylene block polymers, etc. Amounts effective to provide a stable, aqueous formulation will be used, usually in the range of from about 0.1%(w/v) to about 5%(w/v), more preferably, 0.1%(w/v) to about 1%(w/v). The use of non-ionic surfactants permits the formulation to be exposed to shear and surface stresses without causing denaturation of the protein. For example, such surfactant-containing formulations are employed in aerosol devices such as those used in pulmonary dosing and needleless jet injector guns.

Buffers include phosphate, Tris, citrate, succinate, acetate, or histidine buffers. Most advantageously, the buffer is in the range of about 2 mM to about 50 mM. The
5 preferred buffer is a sodium citrate buffer.

A preservative is included in the formulation to retard microbial growth and thereby allow "multiple use" packaging of the hGH. Preservatives include phenol, benzyl
10 alcohol, meta-cresol, methyl paraben, propyl paraben, benzalconium chloride, and benzethonium chloride. The preferred preservatives include 0.2-0.4%(w/v) phenol and 0.7-1%(w/v) benzyl alcohol.

15 Suitable pH ranges, adjusted with buffer, for aqueous hGH formulation are from about 4 to 8, more preferably about 5.5 to about 7, most advantageously 6.0. Preferably, a buffer concentration range is chosen to minimize deamidation, aggregation, and precipitation of hGH.

20 Mannitol may optionally be included in the aqueous hGH formulation. The preferred amount of mannitol is about 5 mg/ml to about 50 mg/ml. As an alternative to mannitol, other sugars or sugar alcohols are used, such as lactose,
25 trehalose, stachiose, sorbitol, xylitol, ribitol, myo-inositol, galactitol, and the like.

Neutral salts such as sodium chloride or potassium chloride are optionally used in place of sugars or sugar
30 alcohols. The salt concentration is adjusted to near isotonicity, depending on the other ingredients present in the formulation. For example, the concentration range of NaCl may be 50-200 mM, depending on the other ingredients present.

35 In a preferred embodiment, the formulation of the subject invention comprises the following components at pH 6.0.

	<u>Ingredient</u>	<u>Quantity (mg)</u>
	hGH	5
	Sodium Chloride	8.8
	Polysorbate 20	2.0
5	Sodium citrates	2.5
	Phenol	2.5
	Sterile water	1 ml

It will be understood that the above quantities are
10 somewhat flexible within ranges, as set forth in more
detail above, and that the materials are interchangeable
within the component categories. That is, polysorbate 80,
or a poloxamer, may be substituted for polysorbate 20, a
succinate or acetate buffer could instead be employed, and
15 alternative preservatives and different pHs could be used.
In addition, more than one buffering agent, preservative,
sugar, neutral salt, or non-ionic surfactant may be used.
Preferably, the formulation is isotonic and sterile.

20 In general, the formulations of the subject invention
may contain other components in amounts not detracting from
the preparation of stable forms and in amounts suitable for
effective, safe pharmaceutical administration. For
example, other pharmaceutically acceptable excipients well
25 known to those skilled in the art may form a part of the
subject compositions. These include, for example, various
bulking agents, additional buffering agents, chelating
agents, antioxidants, cosolvents and the like; specific
examples of these could include trimethylamine salts ("Tris
30 buffer"), and disodium edetate.

EXPERIMENTAL EXAMPLES

A. Assay Methods

35

Anion exchange chromatography (HPIEC) was run on a TSK
DEAE 5PW column (1.0 X 7.5 cm) at 45°C with a flow rate of
0.5 ml/min. The column was equilibrated in 50 mM potassium
phosphate, pH 5.5, containing 10%(w/v) acetonitrile.

Elution was performed using a 25 minute gradient from 50-100 mM potassium phosphate, pH 5.5 with constant 10%(w/v) acetonitrile. The column load was 83 µg of protein.

Detection was at 230 nm.

5

Nondenaturing size exclusion chromatography was run on a TSK 2000 SWXL column in 50 mM sodium phosphate, pH 7.2 containing 150 mM sodium chloride. The flow rate was 1 ml/min, with a 50-75 µg column load and detection at either

10 214 and 280 nm.

Denaturing size exclusion chromatography was run on a Zorbax GF250 column in 200 mM sodium phosphate, pH 6.8-7.2/0.1% SDS. The flow rate was 1.0 ml/minute, with a with a 50-75 µg column load and detection at either 214 and 280 nm.

15

B. Formulation Preparation

20

In general, aqueous hGH formulation samples for analysis in these experimental examples were prepared by buffer exchange on a gel filtration column. The elution buffer contained either sodium chloride or mannitol, buffer and the non-ionic surfactant in their final ratios. This resulting solution was diluted to a desired hGH concentration and the preservative was added. The solution was sterile filtered using a sterilized membrane filter (0.2 micron pore size or equivalent) and filled into sterile 3 cc type 1 glass vials, stoppered and sealed with aqueous-type butyl rubber stoppers and aluminum flip-off type caps.

25

30

The aqueous hGH formulation used in the experimental examples consisted of 5.0 mg somatropin (Genentech, Inc.), 45.0 mg mannitol, 2.5 mg phenol, 2.0 mg polysorbate 20, and 2.5 mg sodium citrate, pH 6.0, per ml of solution. The lyophilized formulation used as a reference for comparison in the examples consisted of 5.0 mg somatropin, 1.7 mg glycine, 45.0 mg mannitol, 1.7 mg sodium phosphate, 9 mg

35

benzyl alcohol per ml sterile solution after reconstitution.

C. Example I

5

Chemical Stability of the Aqueous Formulation

Vials of the hGH aqueous formulation (lots 12738/55-102 and 12738/55-105) were incubated at either recommended storage temperatures of 2-8°C, or elevated storage temperatures of 15°C, or 25°C, and then removed at various time points and assayed for changes in pH, color and appearance, and protein concentration. In addition, samples were incubated at 40°C in order to study degradation patterns under extreme stress conditions. Degradation patterns for the aqueous formulation were also compared to the known degradation patterns for lyophilized growth hormone.

20 After storage at 2-8°C for up to one year, the aqueous formulation showed insignificant changes in pH, color and appearance, and protein concentration. Nondenaturing size exclusion HPLC performed on samples stored for up to one year at 2-8°C showed no significant aggregation of the drug product (Figure 1). This result is unexpected in light of the teaching of U.S. 5,096,885 that glycine contributes to preventing aggregation in the lyophilized preparation.

30 At temperatures above 8°C, little or no changes in pH or protein concentration were observed over time. Visual inspection revealed an increase in opalescence with time for samples stored at 40°C. This change was minimal during storage at 15-25°C and has not been observed during 2-8°C storage.

35

The amount of degradation product was calculated as an area percentage of the total hGH area of the chromatogram. The rate constant for each reaction was then calculated by subtracting the percentage of degradation product from

100%, taking the \log_{10} , and plotting against the time in days. The slope of a straight line to fit these data was used as the reaction constant (k). Arrhenius analysis was done by plotting the natural logarithm (ln) of the absolute value of each calculated reaction rate constant at 15, 25, and 40°C as a function of the inverse absolute temperature and then extrapolating to 5°C. Arrhenius and real time rate analysis (Figure 2) of data from the size exclusion HPLC indicate that the amount of growth hormone aggregation after 18 months of storage will be less than 1%(w/v).

Anion exchange HPLC analysis performed on the aqueous hGH formulation stored at 40°C indicated an increase in acidic peaks over 28 days (Figure 3). Three of these peaks, eluting at about 16, 17.5, and 26 minutes, were produced by hGH deamidation at positions 149, 152, and 149 plus 152. Arrhenius and real time rate analysis (Figure 4) of data from this method, were plotted as described above, and indicate that the amount of deamidated hGH in these lots after 18 months of storage at 2-8°C will be about 9%(w/v). This includes an initial amount of about 2.4%(w/v) deamidated hGH at time zero. Values as high as 15%(w/v) deamidation have been reported for other hGH products (Larhammar, H., et al., (1985) Int. J. Pharmaceutics 23:13-23). Although the rate of deamidation is faster in the aqueous state, this rate is minimized at pH 6.0 and below.

D. Example II

Physical Stability of the Aqueous Formulation

Each of six vials of lyophilized growth hormone were reconstituted with 1 ml bacteriostatic water for injection (BWFI) U.S.P. After dissolving, the contents were transferred to 3 cc vials, stoppered, and capped to provide the same configuration as that for the aqueous formulation. The six vials of the hGH aqueous formulation and six vials of reconstituted lyophilized hGH were

vigorously shaken top to bottom in a horizontal fashion on a Glas-Col Shaker-in-the-Round at 240 jolts per minute using a stroke setting of 2.5, giving a horizontal displacement of 8 ± 1 cm for up to 24 hours at room temperature to assess the effects of agitation on physical stability of the hGH aqueous formulation. All twelve samples were placed in a straight line on the shaker to assure that they were all exposed to the same force for each formulation. Two vials were removed for assays at 30 minutes, 6 hours, and 24 hours.

The results are displayed in Table I. Agitation produced very little change in the visual clarity of the aqueous formulation. There was no change in the content of total growth hormone monomer as detected by a nondenaturing size exclusion HPLC assay. This assay detects noncovalent aggregates, which are completely dispersed by SDS in a denaturing size exclusion HPLC assay.

By comparison, these results also demonstrated that the reconstituted lyophilized product was more sensitive to treatment, even after only 30 minutes of shaking. This sensitivity is typical for all currently available formulations of hGH, other than the aqueous formulation of the instant invention. The inclusion of the non-ionic surfactant is the most important factor in preventing this phenomenon from occurring.

Table I. Effects of Agitation at Room Temperature on hGH Aqueous Formulation vs. Reconstituted Lyophilized Formulation

Sample	Color/Appearance	% HPSEC Monomer	% Soluble Protein	% Total ¹ Monomer
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Unshaken

Aqueous	clear/colorless	99.7	ND	ND
Aqueous	clear/colorless	99.9	ND	ND
Lyophilized	clear/colorless	99.0	100	99.0
Lyophilized	clear/colorless	ND	ND	ND

Shaken**0.5 hr**

Aqueous	very slightly opalescent/colorless	99.9	100	99.9
Aqueous	very slightly opalescent/colorless	100.0	100	100.0
Lyophilized	slightly opalescent/colorless	93.6	100	93.6
Lyophilized	clear/colorless	92.8	100	92.8

Shaken**6 hr**

Aqueous	slightly opalescent/colorless	99.9	100	99.9
Aqueous	opalescent/colorless	99.8	100	99.8
Lyophilized	very opalescent/yellow to brown	80.5	73	58.8
Lyophilized	very opalescent/yellow to brown	72.7	61.7	44.9

Table I. (continued)

Sample	Color/Appearance	% HPSEC Monomer	% Soluble Protein	% Total ¹ Monomer
Shaken				
24 hr				
Aqueous	slightly opalescent/ colorless	99.8	100	99.8
Aqueous	clear/colorless	99.8	ND	ND
Lyophilized	very cloudy/ yellow to brown	60.6	21.5	13.0
Lyophilized	very cloudy/ yellow to brown	56.7	14.8	8.4

¹ Total monomer = (% monomer X % soluble protein)/100

5

E. Example III

Preservative Effectiveness in the Aqueous Formulation

10 Samples of hGH aqueous formulation were subjected to
bacterial challenge according to an abbreviated challenge
using the standard U.S.P. test. In this test, a suspension
of either *E. coli* or *S. aureus* was added to an aliquot of
hGH aqueous formulation to give a final concentration of
15 bacteria between 10⁵ to 10⁶ CFU/ml. Viable bacteria
remaining in the tubes were counted immediately and after 4
and 24 hours incubation at 20-25°C. The percentage change
in the concentration of the microorganisms during the
challenge was calculated according to the following
20 equation:

$$\% \text{ initial titer} = \text{titer at } T=X \text{ hours} \times 100$$

$$\text{titer at } T=0$$

The results of this experiment indicated that for two species of bacteria, concentrations of viable bacteria were reduced to less than 0.01% of the initial concentrations after 24 hours.

5

F. Example IV

Substitution of Mannitol with Salt

10 In this experiment aqueous formulations of hGH were compared that varied in concentrations of salt, mannitol, and non-ionic surfactant. All formulations contained 5 mg/ml hGH/ 0.25%(w/v) phenol/ 10 mM sodium citrate, pH 6.0. Samples were stored 3-4 months at 2-8°C. Figure 5
15 indicates the percentage monomer present in the indicated formulations. The Table below indicates the composition of each formulation. These results demonstrate the unexpected stability of hGH in a formulation in which mannitol has been substituted with a neutral salt in the presence of a
20 surfactant.

Table 3. Formulations Tested in Figure 5

Formulation #	Composition
42	0.1%(w/v) polysorbate 20 50 mM mannitol
47	0.1%(w/v) poloxamer /188 0.1 M NaCl
51	0.5%(w/v) polysorbate 20 50 mM mannitol
52	0.1%(w/v) poloxamer 188 50 mM mannitol
53	0.1%(w/v) poloxamer 184 50 mM mannitol
60	0.2%(w/v) polysorbate 20 0.1 M NaCl
61	0.2%(w/v) polysorbate 20 0.05 M NaCl
62	0.2%(w/v) polysorbate 20 0.15 M NaCl
63	0.2%(w/v) polysorbate 20 50 mM mannitol

We claim:

1. A stable pharmaceutically acceptable aqueous formulation of human growth hormone comprising:

- a) human growth hormone,
- b) a buffer
- c) a non-ionic surfactant,
- d) optionally, mannitol,
- e) optionally, a neutral salt, and
- f) optionally, a preservative.

2. The formulation of claim 1 wherein the non-ionic surfactant is present in the range of about 0.1%(w/v) to about 1%(w/v).

3. The formulation of claim 1 wherein the non-ionic surfactant is a poloxamer.

4. The formulation of claim 1 wherein the non-ionic surfactant is a polysorbate.

5. The formulation of claim 3 wherein the poloxamer is poloxamer 188 or poloxamer 184.

6. The formulation of claim 4 wherein the polysorbate is polysorbate 20 or polysorbate 80.

7. The formulation of claim 1 wherein the concentration of mannitol is about 5 mg/ml to about 50 mg/ml.

8. The formulation of claim 1 wherein the buffer is a citrate buffer.

9. The formulation of claim 1 wherein the buffer concentration is about 2 mM to about 50 mM.

10. The formulation of claim 1 wherein the buffer is selected from the group consisting of phosphate, Tris, succinate, acetate, or histidine buffers.

11. The formulation of claim 1 wherein the formulation is sterile.

12. The formulation of claim 1 wherein the formulation is isotonic.

13. The formulation of claim 1 wherein the neutral salt is sodium chloride.

14. The formulation of claim 1 wherein the preservative is selected from the group consisting of phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, benzalconium chloride, and benzethonium chloride.

15. An aqueous hGH formulation comprising 5 mg/ml hGH, 8.8 mg/ml sodium chloride, 2.0 mg/ml polysorbate 20, 2.5 mg/ml sodium citrate, and 2.5 mg/ml phenol, at pH 6.0.

16. A method of preventing denaturation of human growth hormone aqueous formulations comprising mixing human growth hormone and a non-ionic surfactant in the range of 0.1-5%(w/v).

17. The method of claim 16 wherein the non-ionic surfactant is a poloxamer.

18. The method of claim 16 wherein the non-ionic surfactant is a polysorbate.

19. The method of claim 17 wherein the poloxamer is poloxamer 188 or 184.

20. The method of claim 18 wherein the polysorbate is polysorbate 20 or polysorbate 80.

21. A method of preventing denaturation of human growth hormone aqueous formulations stored for six to 18 months at 2-8°C comprising mixing human growth hormone and a non-ionic surfactant in the range of 0.1-5%(w/v).

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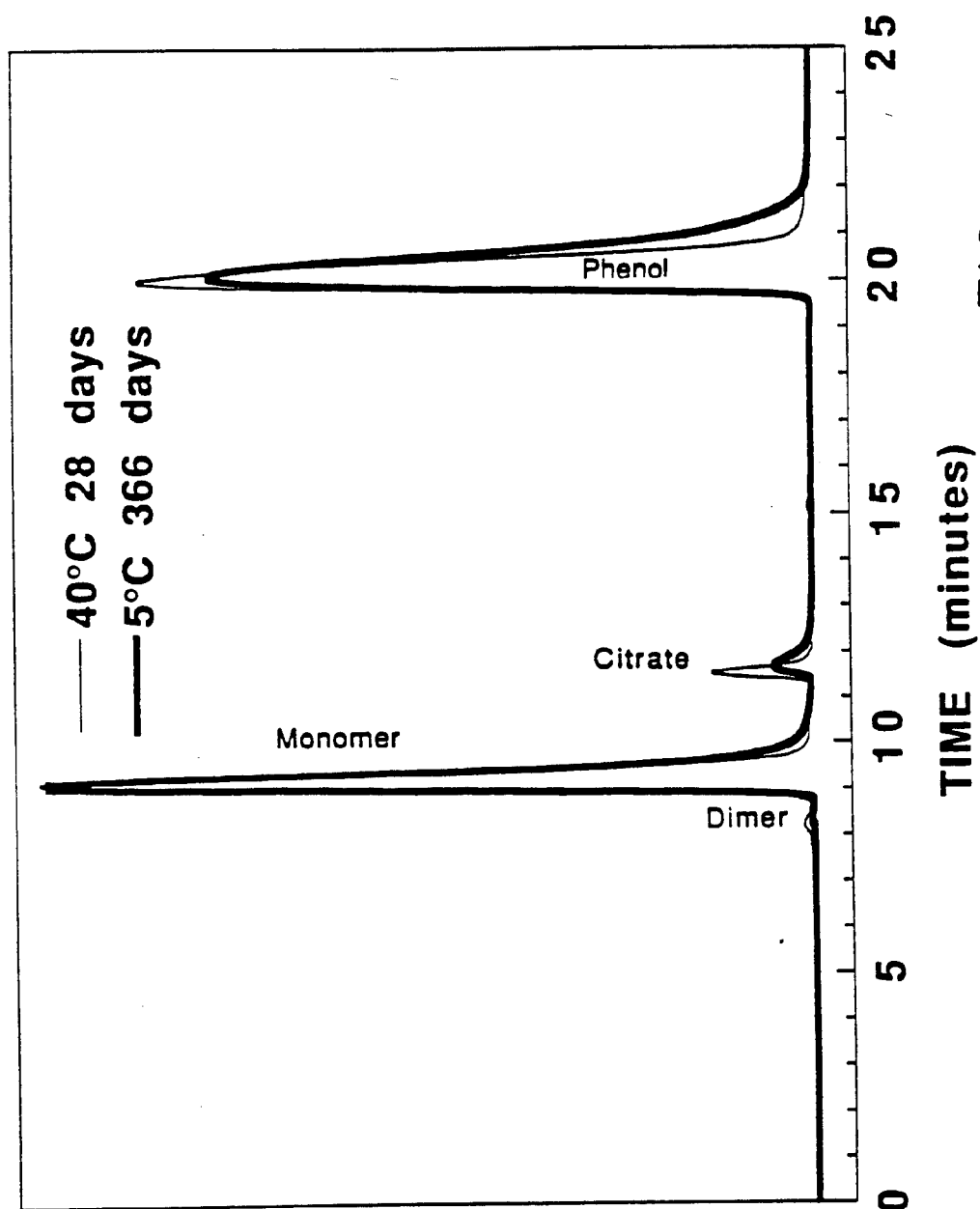


FIG. 1

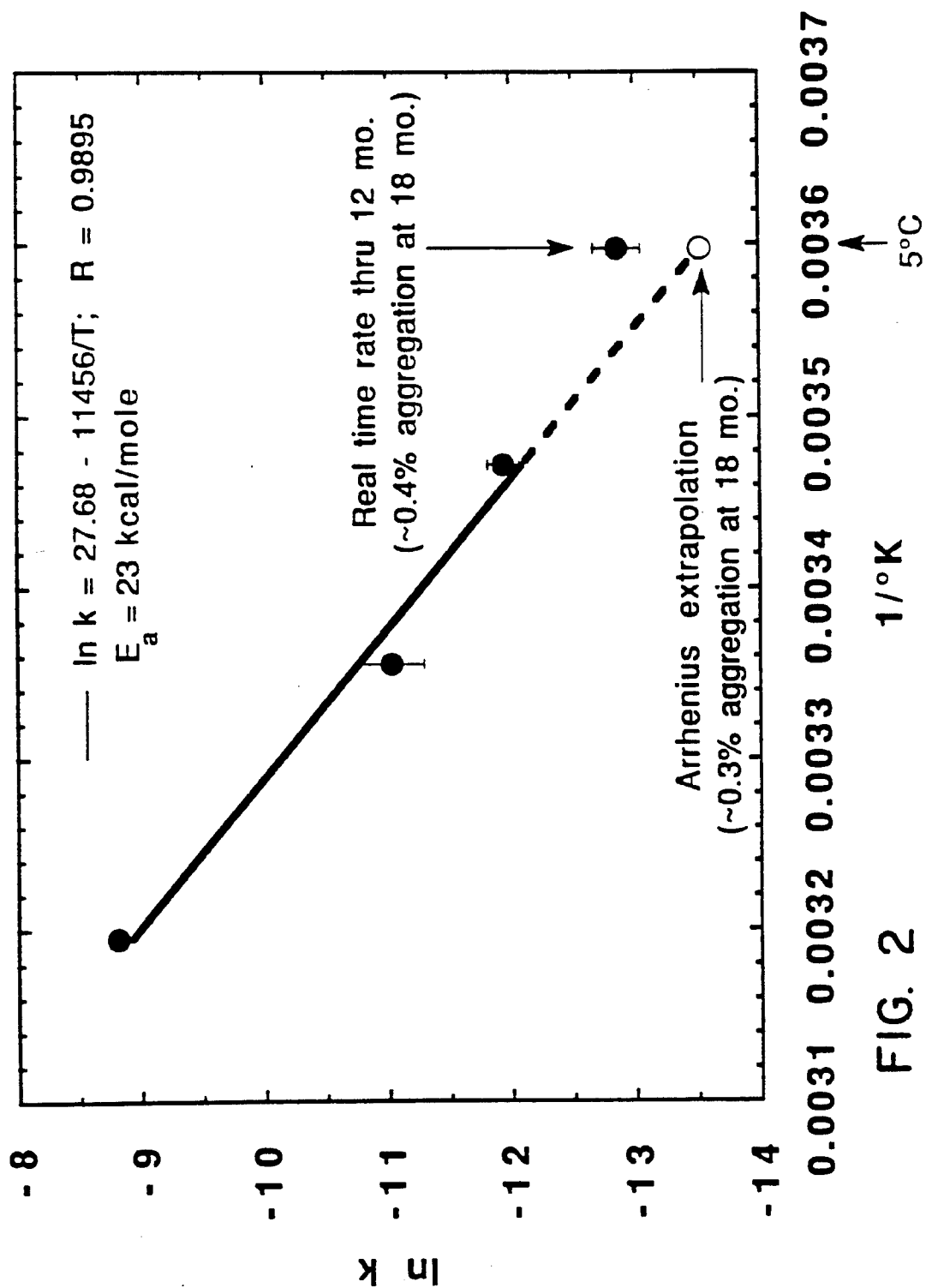


FIG. 2

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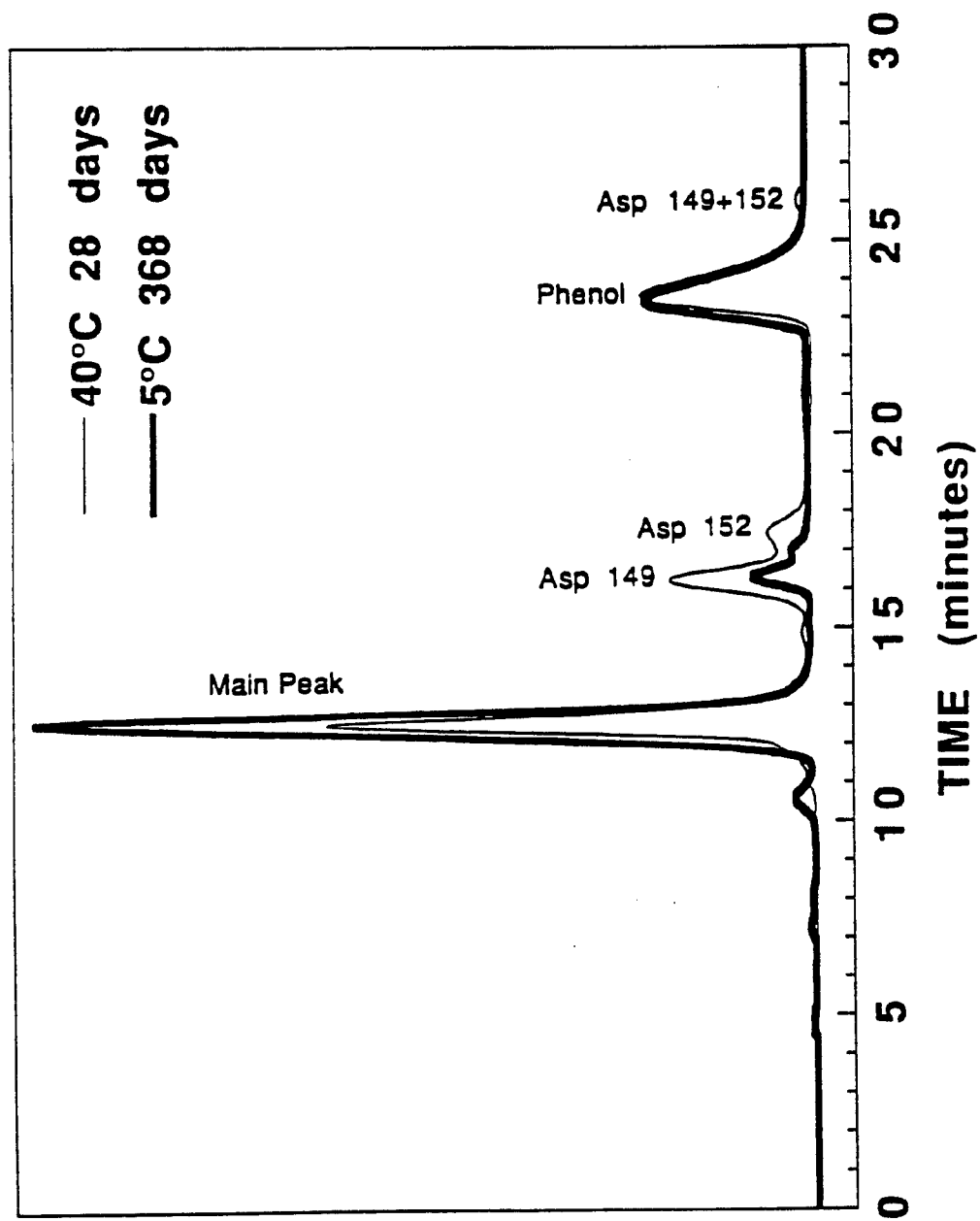
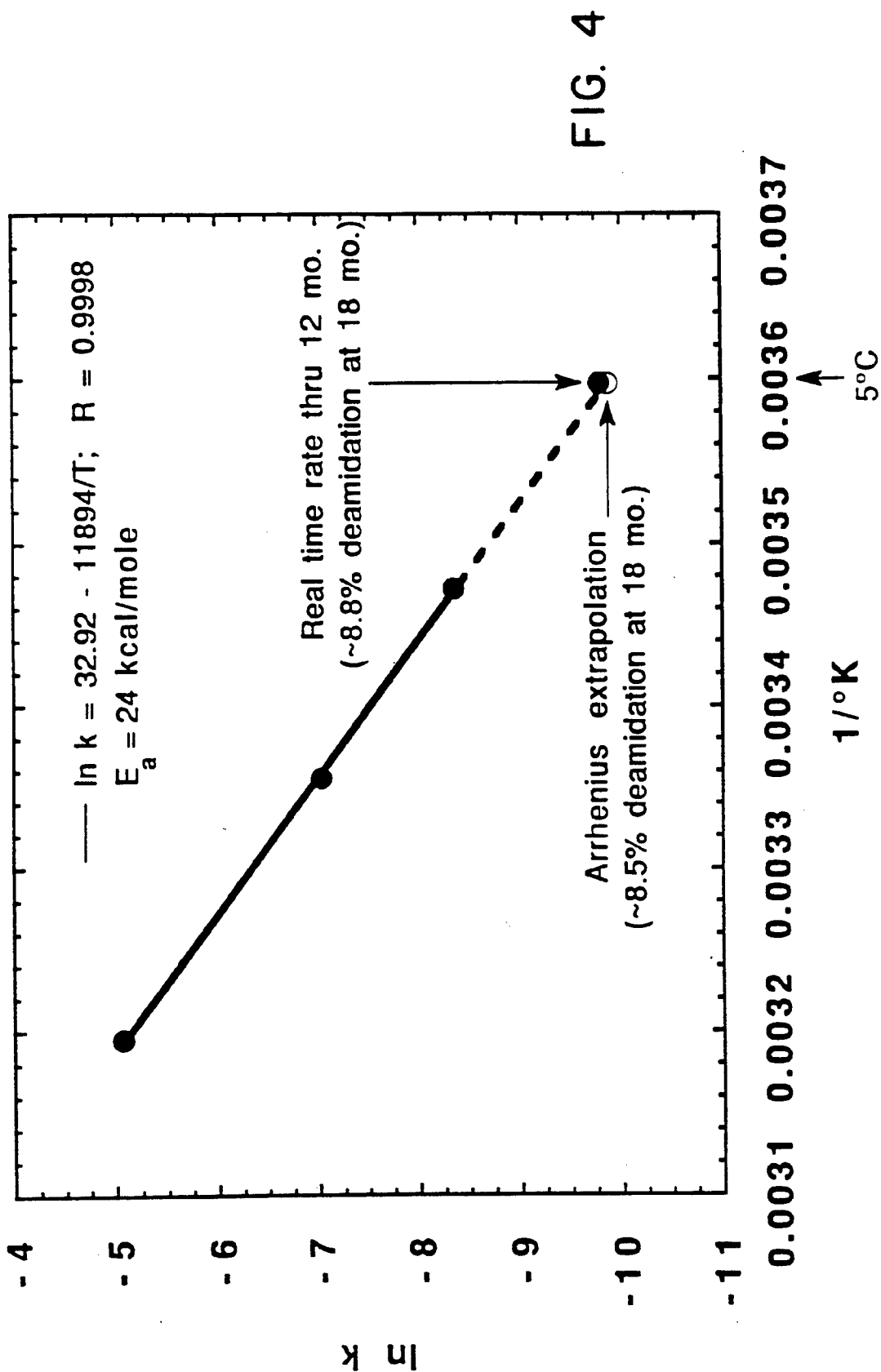


FIG. 3



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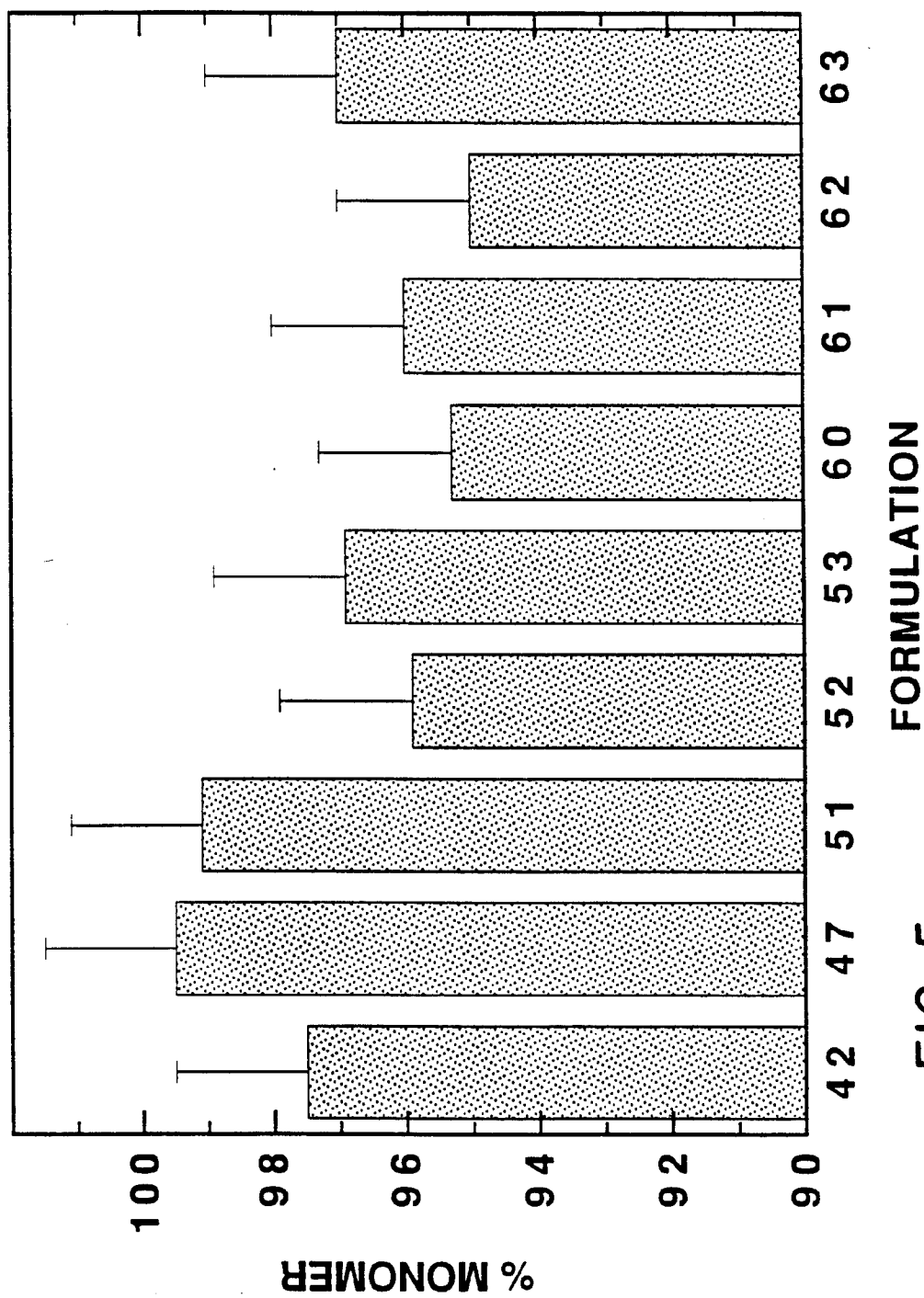


FIG. 5

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 93/07149

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K37/02 A61K47/10 A61K47/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 211 601 (INTERNATIONAL MINERALS AND CHEMICAL CORPORATION) 25 February 1987 cited in the application see claims see page 5, line 12 see page 6, line 31 see page 9, line 4 - line 5 see page 9, line 14 - line 18 see examples ---	1-3,5, 10-13
X	EP,A,0 131 864 (HOECHST) 23 January 1985 see claims 1-5,7,11-13 see page 4, line 15 - line 23 see page 5, line 27 see examples --- -/--	1-3,5, 8-14,16, 17,19,21



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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